General

Guideline Title

Mannitol dry powder for inhalation for treating cystic fibrosis.

Bibliographic Source(s)

National Institute for Health and Clinical Excellence (NICE). Mannitol dry powder for inhalation for treating cystic fibrosis. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Nov. 58 p. (Technology appraisal guidance; no. 266).

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Mannitol dry powder for inhalation is recommended as an option for treating cystic fibrosis in adults:

- Who cannot use recombinant human deoxyribonuclease (rhDNase) because of ineligibility, intolerance or inadequate response to rhDNase and
- Whose lung function is rapidly declining (forced expiratory volume in 1 second [FEV1] decline greater than 2% annually) and
- For whom other osmotic agents are not considered appropriate.

People currently receiving mannitol whose cystic fibrosis does not meet the above mentioned criteria should be able to continue treatment until they and their clinician consider it appropriate to stop.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Cystic fibrosis

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Family Practice

Internal Medicine

Pulmonary Medicine

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Respiratory Care Practitioners

Guideline Objective(s)

To assess the clinical effectiveness and cost-effectiveness of mannitol dry powder for inhalation for treating cystic fibrosis

Target Population

Adults (18 years and above) with cystic fibrosis

Interventions and Practices Considered

Mannitol dry powder for inhalation

Major Outcomes Considered

- Clinical Effectiveness
  - Change in absolute forced expiratory volume in 1 second (FEV1) over 26 weeks compared to control
  - FEV1 change from baseline (mL) compared to control
  - Change in FEV1 by existing recombinant human deoxyribonuclease (rhDNase) treatment
  - Proportion of subjects who "respond" on the basis of FEV1
  - Proportion of subjects who "respond" on the basis of quality of life
  - Pulmonary exacerbations
  - Quality of life
  - Exercise tolerance
  - Days on intravenous antibiotics, rescue oral or inhaled antibiotics
  - Hospital days due to pulmonary exacerbations

- Safety profile (adverse events, changes in haematology or biochemistry profile)
- Sputum weight

- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The Evidence Review Group (ERG) report for this appraisal was prepared by Kleijnen Systematic Reviews (see the "Availability of Companion Documents" field).

Clinical Effectiveness

State Objective of Systematic Review. Provide Description of Manufacturer's Search Strategy and Comment on Whether the Search Strategy Was Appropriate. If the Manufacturer Did Not Perform a Systematic Review, Was This Appropriate?

An evidence based checklist for the Peer Review of Electronic Search Strategies (PRESS), developed by McGowan, was adapted to serve as a template for this critique. The submission was checked against the Single Technology Appraisal (STA) specification for manufacturer/sponsor submission of evidence, to show that retrieval could be improved. The ERG created a number of comparison search strategies and reran many of those created by the manufacturer. The ERG search strategies are presented in Appendix 2 of the ERG report (see the "Availability of Companion Documents" field). In all but one case, the ERG was not able to screen search results due to time constraints, and therefore can only show the numerical differences in the numbers of references retrieved between manufacturer and ERG searches without a definitive indication that relevant studies were missed.

The manufacturer's statement states that search was carried out in two "phases"; phase one included the entire cystic fibrosis (CF) population, and phase two only the adults. However since both first and second phase searches were identical and were carried out on the same day, the ERG critiqued them as one.

The databases searched were in line with NICE's guidance: Medline, Medline In-Process, EMBASE, and Cochrane Library, with additional searches using ClinicalTrials.gov, the NICE website and a search of Pharmaxis' data using their European Medicines Agency (EMA) license application for Bronchitol. The providers for each database were listed, as were the dates of searching. Limited details of the date span of searches were reported. The start date for each database was accurate but the end date was not for some databases (see Section 4.1.1.1 of the ERG report).

The strategies were clearly structured into population and intervention facets with the addition of a study design filter, when supported by the database. While fundamentally sound in construction, sensitivity would have been improved by the inclusion of synonyms for mannitol and CF. The ERG identified several relevant synonyms for the population and intervention, including subject headings in Medline and EMBASE. By combining truncation and a wildcard in mannitol to create the search term "mann?t$" (valid in Medline and EMBASE), many relevant synonyms would have been retrieved without impacting on specificity. The Chemical Abstracts Service (CAS) registry number for mannitol would also have been a useful addition to the strategy.

The major criticism of this search was the use of an unreferenced randomised controlled trials (RCT) filter in the Medline, Medline In-Process and EMBASE searches. There were two reasons why the ERG felt this was problematic. Firstly, the number of references retrieved, without the inclusion of an RCT, could easily be screened by a reviewer (n=150 in EMBASE, n=77 in Medline and n=2 in Medline In-Process). The second reason was it would be preferable to incorporate an objectively derived RCT filter. A selection of objectively derived study design filters/hedges can be easily identified for both OvidSP Medline and OvidSP EMBASE, by using the Information Specialists' Sub-Group (ISSG) Search Filter Resource.

The ERG could not fully reproduce the manufacturer searches, as the strategies in the manufacturer's submission (MS) did not report the field tags

used for the Medline, Medline In-Process and EMBASE searches. The ERG assumed the basic keyword search function was employed, which applies the .mp tag by default. Comparison of the re-run manufacturer searches with those reported in the MS highlighted some inconsistencies in the results that could not be explained by changes in the database contents in the intervening period.

The ERG created Medline and EMBASE search strategies using subject headings, synonyms and an objectively derived RCT filter. The results of this ERG search were compared with the updated manufacturer searches (see Table 1 in the ERG report [see the "Availability of Companion Documents" field]) and highlighted the importance of the use of an objectively derived RCT filter. The ERG concluded that relevant studies might have been missed due to the basic filter employed by the manufacturer.

The Cochrane Library search had similar limitations as the Medline and EMBASE in terms of lack of synonyms and truncation. However the ERG's search, which included additional synonyms, retrieved only slightly more hits on CENTRAL and no more hits on Cochrane Database of Systematic Reviews (CDSR) than updated searches using the manufacturer's strategy.

The MS stated that an additional search was carried out on ClinicalTrials.gov. The ERG created a new search for this resource using the synonyms from the previous clinical effectiveness searches and retrieved the same number of hits as the manufacturer. The MS did not include details of the search terms used to search the NICE website or the Pharmaxis in-house resources, therefore the ERG was unable to comment on these searches.

State the Inclusion/Exclusion Criteria Used in the Study Selection and Comment on Whether They Were Appropriate

Review of Mannitol Studies

Inclusion Criteria

First Phase

Population: Patients with cystic fibrosis
Interventions: Bronchitol or Bronchitol
Study design: Randomised clinical trial
Language restrictions: English language only

Exclusion Criteria

Second Phase

Population: Paediatric or adolescent patients only
Interventions: Doses of Bronchitol/Bronchitol not at therapeutic dose (i.e., not at ≈ 400 mg twice daily [BD]); different formulation to that being licensed.

Mixed Treatment Comparison

Inclusion Criteria

- Patients with CF diagnosed clinically or by sweat and genetic testing, including all degrees of disease severity
- Treatment with hypertonic saline or Bronchitol (~ 400 mg BD)
- Prospective randomised controlled trials (RCTs)

Exclusion Criteria

- None

See Chapters 4.1.1 and 4.1.2 of the ERG report for more information.

Cost-Effectiveness

The search concepts were stated as "cost effectiveness" combined with "cystic fibrosis". This appeared to be a revised approach, as the first search contained a mannitol facet as well. The original search retrieved 0 hits. At that point, the manufacturer expanded the search parameters by removing the mannitol facet. The ERG felt the alteration of search strategy should have been reported in the main report text as well as the appendix.

The manufacturer searched PubMed and the Centre for Reviews and Dissemination (CRD) databases. The PubMed search covered Medline and Medline In-Process, and the CRD databases encompassed the National Health Service Economic Evaluation Database (NHS EED). The MS stated that Cochrane Collaboration was searched; no details of a search strategy were reported, but the MS states the search retrieved 2 hits. The

ERG was unable to reproduce this search. Although the MS and clarification response (CR) reported several EMBASE search strategies for previous sections, the CR stated that EMBASE and EconLIT were not searched for the cost-effectiveness section, due to lack of access. The databases are required for inclusion by the NICE Specification for the MS. It is important to search EMBASE as well as PubMed due to the differences in their coverage. The largest component of PubMed is Medline and approximately 1,800 of the journals indexed in EMBASE are not indexed in Medline. The ERG felt that EMBASE would have been particularly useful for this submission, due to EMABSE's pharmaceutical and European focus to its content.

The date and span of searching was reported for PubMed and CRD, but this information was not provided for the Cochrane Collaboration/Library search. The searches were reported clearly to enable replication.

The first PubMed search was well constructed using Boolean logic and correctly combined an intervention facet (mannitol) with a population facet (cystic fibrosis [CF]) and a study design facet (cost-effectiveness). The ERG felt that the mannitol facet could have been improved by incorporating truncation, synonyms and a CAS number. The CF facet did not use any free text terms, instead relying solely on a subject heading. Relying solely on subject headings in search facets is not good practice as highlighted in the Cochrane Handbook which cautions searchers against the assumption that all articles will be indexed correctly or in line with the searcher's expectations. A wide variety of text terms should be used to supplement subject headings.

The second search removed the mannitol facet to increase sensitivity. The third search was almost identical to the second except that it used the NOT operator to remove all articles with "screening" or "diagnosis" in the title or abstract. The Cochrane Handbook recommends that the NOT operator should be avoided where possible due to the possible removal of relevant records. In this case, it could be foreseen that relevant cost-effectiveness studies might reference screening or diagnosis in the title or abstract and thus be missed. This did not impact negatively on retrieval because this search's results were a subset of search two and the MS stated that results from the second search were screened as well, therefore the ERG was unclear why the third search was undertaken.

An unreferenced cost-effectiveness (CE) filter was used in these searches. It contained this section: "cost effectiveness"[Title/Abstract] OR cost[Title/Abstract]. The former phrase is rendered redundant by the latter. The PubMed database provides cost and economic filters that have been adapted from objectively derived filters and utilising one or both of those would have been more appropriate for these searches.

An English language and date limit (1990 onwards) were added to the PubMed searches. This appeared to contradict the manufacturer's opening statement of intent in this chapter to "identify any existing cost-effectiveness studies in the field of CF". No rationale was given for the date limit; however, some was given for the language in the CR. The manufacturer conducted a separate wave of searches for studies written in five other European languages, the second search inexplicably retrieving fewer studies than the third, given that the third was simply a subset of the second. The ERG was unclear why the manufacturer decided again in the second search to limit to just five languages as this might have introduced bias into the results. The Cochrane Handbook advises against searching using language limits and afterwards to make decisions about including non-English studies on a case-by-case basis.

Table 2 of the ERG report illustrates how using a more sophisticated search strategy and CE filter, removal of unnecessary limits and searching all important databases (e.g., EMBASE), increased the retrieval many times over. The ERG considered it very likely that relevant CE studies may have been missed; however, the ERG was unable to screen the additional references due to time constraints.

State the Inclusion/Exclusion Criteria Used in the Study Selection and Comment on Whether They Were Appropriate

The MS did not include any statement on the inclusion and exclusion criteria in the study selection for the cost effectiveness review.

Comment

The ERG cannot comment on the inclusion and exclusion criteria as they were not described in the MS.

Number of Source Documents

Clinical Effectiveness

- Two randomised controlled trials (RCTs)

Cost-effectiveness

- The manufacturer's submission identified ten cost-effectiveness studies.
- The manufacturer presented an economic model.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Meta-Analysis of Randomized Controlled Trials

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The Evidence Review Group (ERG) report for this appraisal was prepared by Kleijnen Systematic Reviews (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Describe and Critique the Manufacturer's Approach to Validity Assessment for Each Relevant Trial

Table 8 of the ERG report describes quality assessment of included randomised controlled trials (RCTs).

Comment

Generally, the ERG agrees with the reported quality assessment. Regarding outcomes reported, although all outcomes were reported for the total population, they were not reported for the two populations of interest for this appraisal.

Describe and Critique the Statistical Approach Used within Each Relevant Trial

Table 9 of the ERG report describes statistical analyses in the relevant RCTs.

Comment

Apart from the fact that analysis were not presented separately for the two populations of interest for this appraisal, the statistical analyses in both studies seem sound.

Describe and Critique the Manufacturer's Approach to Outcome Selection within Each Relevant Trial

The key outcomes from the two included studies are described in Table 10 of the ERG report.

Comment

All relevant outcomes as described in the scope, except for mortality, are listed in Table 10 of the ERG report. Mortality was not assessed in either trial, despite it being mentioned as an included outcome in the statement of the decision problem. No justification in the manufacturer's submission (MS) was provided for this omission. However, the main problem relating to the outcomes reported is the fact that only lung function is reported in the MS for one of the relevant populations for this appraisal: adult recombinant human deoxyribonuclease (rhDNase) users. In response to the clarification letter, the ERG received data for both populations, adult rhDNase users and adults who are ineligible, intolerant, or inadequately responsive to rhDNase, for change in forces expiratory volume in 1 minute (FEV1) (graphs only) and exacerbations. No other data were provided, despite the ERG request for all relevant data for the specific populations. This means the ERG has no data relating to the relevant populations for the following outcomes: mortality, respiratory symptoms, exercise tolerance, adverse events and quality of life.

Where Appropriate, Describe and Critique Any Meta-analysis, Indirect Comparisons and/or Mixed Treatment Analysis Carried Out by the Manufacturer

The meta-analyses in the MS comprised the pooling of data from the two included studies for three outcomes: % predicted FEV1, FEV1 responders and per patient per year rate of protocol defined pulmonary exacerbations (PDPE). These outcomes were considered relevant for the economic model.

None of these analyses included data for the two relevant populations for this appraisal.

Indirect and/or mixed treatment comparisons were deemed inappropriate.

Comment

Where possible the ERG has reported data for the relevant populations (see Table 7, Section 4.2.1 of the ERG report). In addition, an indirect comparison of mannitol versus hypertonic saline is reported in Section 4.2.7 of the ERG report.

When data from the two included RCTs were combined, the ERG pooled the relative effects of each study. In the MS results were combined within each treatment arm and then compared between arms. However, this approach in the MS does not preserve randomisation.

See Sections 4.2 and 4.3 of the ERG report (see the "Availability of Companion Documents" field) for additional information.

Cost-Effectiveness

Summary and Critique of Manufacturer's Submitted Economic Evaluation by the ERG

An overall summary of the *de novo* economic model developed by the manufacturer is given in Table 13 of the ERG report.

The ERG has assessed the manufacturer's economic evaluation using the Philips et al. checklist for quality assessing decision analytic models. This is shown in Appendix 3 of the ERG report.

Model Structure

The model that was developed for the current economic evaluation is a patient-level simulation Markov model, which means that the progression of each individual patient is modelled, rather than the progression of a whole patient cohort at once. As patients move through the model one at a time, the model memorises specific patient characteristics like lung function, age, and body mass index (BMI), which are updated over time. These characteristics are taken into account when determining the transition probabilities and thus the path through the tree. A schematic presentation of the relationship between treatment, time, clinical endpoints and economic endpoints is shown in Figure 1 of the ERG report.

The following health states can be distinguished in the model:

- Cystic fibrosis (CF)
- CF with improved respiratory symptoms
- Lung transplant
- Death due to CF
- Death due to unrelated cause

Comment

The Markov states and transitions defined in the model describe more the clinical studies with mannitol than the natural disease course of cystic fibrosis. In general, relative health states (such as improved respiratory symptoms) should be avoided. However, since the Markov model was used for individual patient simulation, with transitions, events, and utilities dependent on the individual's absolute FEV1 % predicted, the ERG considers the current model structure appropriate for the research question.

Sensitivity Analyses

The manufacturer assessed the various uncertainties in the economic evaluation through deterministic sensitivity analysis, scenario analysis and probabilistic sensitivity analysis. While the first two show which parameters and assumption have the largest impact on the model outcomes, the latter shows the overall uncertainty around the incremental cost effectiveness ratio (ICER). Unfortunately, the manufacturer provided all sensitivity analyses and scenario analyses based on the original model, for which the analysis of the trial data were done for all adult patients, instead of separately for the two licensed populations. Consequently, the main relevance of these analyses is not the absolute ICERs they present, but rather the order of magnitude of the impact on the ICERs, since the ERG assumes that this relative impact will hold in the ERG base case analyses based on the correct populations. All three type of sensitivity analyses are discussed in the ERG report.

See Chapter 5 of the ERG report for additional information on cost-effectiveness.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites "consultee" and "commentator" organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an "assessment report". Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the "appraisal consultation document" (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE Web site. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the "final appraisal determination" (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Summary of Appraisal Committee's Key Conclusions

Availability and Nature of Evidence

The manufacturer developed a Markov health-state transition model, taking into account individual patient pathways over a lifetime horizon, and modelling 2 treatment options: treatment with inhaled mannitol and treatment without inhaled mannitol. The manufacturer did include hypertonic saline as a comparator. The manufacturer did not use clinical-effectiveness data from the trials presented in the submission other than to obtain baseline values and some transition parameters; instead, the manufacturer derived transition parameters from the literature and from its own commissioned studies, incorporating them into the model using regression analysis. The Committee noted that the structure of the original model

was not a health-state model, but rather was a model of the cystic fibrosis treatment pathway. The Committee acknowledged the changes to the model made by the manufacturer in their response to the appraisal consultation document (ACD), in light of the Evidence Review Group's (ERG's) concerns. The Committee concluded that the cost-effectiveness model was complex and may not adequately reflect the clinical trial data.

Uncertainties Around and Plausibility of Assumptions and Inputs in the Economic Model

The Committee was concerned about the manufacturer's assumptions that any improvement in forced expiratory volume in one second (FEV1) would be maintained throughout the lifetime of the patient, and that it would be directly translated into lower morbidity and mortality rates. It was concerned about the limited number of variables incorporated into the model, and that there were other models of cystic fibrosis that had incorporated a greater variety of variables. The Committee concluded that there was substantial uncertainty surrounding the assumption that FEV1% predicted changed with age and that the use of UK data would have been more appropriate, and that this led to uncertainty about the applicability of the model to the UK population with cystic fibrosis.

Incorporation of Health-Related Quality-of-Life Benefits and Utility Values

The Committee was also aware that the model was sensitive to the baseline utility, with the incremental cost-effectiveness ratio (ICER) increasing as the baseline utility decreased. The Committee noted that adverse events and their effect on quality of life were not incorporated into the model. The Committee was concerned by the use of Health Utility Index 2 (HUI2) data rather than the EQ-5D (a standardised instrument for use as a measure of health outcome). The Committee concluded that it was not convinced that the health-related quality-of-life of patients with cystic fibrosis had been valued with any certainty. The Committee noted that virtually all of the benefit of mannitol was from its modelled extension of life years gained, with very little benefit resulting from improved health-related quality of life.

Have Any Potential Significant and Substantial Health-Related Benefits Been Identified That Were Not Included in the Economic Model, and How Have They Been Considered?

The Committee agreed with the manufacturer's statement at the meeting that the model included all potential benefits associated with mannitol treatment, and that no additional health-related benefits had been identified that had not been adequately captured by the economic model.

Are There Specific Groups of People for Whom the Technology Is Particularly Cost-Effective?

The Committee considered the subgroup defined by rapidly declining lung function (greater than 2% per annum) whose condition was unsuitable for treatment with recombinant human deoxyribonuclease (rhDNase). The Committee noted that any increase in lung function would be proportionally greater, and that mannitol was likely to be more clinically effective in this subgroup, which would consequently decrease the ICER.

What Are the Key Drivers of Cost-Effectiveness?

Factors that would increase the ICERs include alternative assumptions about mortality and the long-term effect of mannitol on lung function. Factors that could decrease the ICERs included the possibility of higher rates of pulmonary exacerbations seen in clinical practice, a rate of compliance reflecting the trials, establishing if there is a link between lung function and quality-of-life utilities, and estimating more realistic utilities associated with mannitol use.

Most Likely Cost-Effectiveness Estimate (Given as an ICER)

The Committee noted that if mannitol treatment was offered only to patients with a rapid decline in lung function, the ICER would most likely be lower than in the whole population because of this group's lower quality of life and lung function, and a greater potential to improve. The Committee concluded that the ICER for mannitol in patients for whom hypertonic saline is not considered appropriate, who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase, and whose lung function is rapidly declining would be under £30,000 per quality-adjusted life-year (QALY) gained. It also took into account the severity of the disease and the importance of treatment options for people with cystic fibrosis who have few alternative options. The Committee concluded that mannitol should be recommended as an acceptable use of National Health Service (NHS) resources as a treatment option in this group.

See Sections 3 and 4 of the original guideline document for details of the economic analysis provided by the manufacturer, the Evidence Review Group comments, and the Appraisal Committee considerations.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Consultee organisations from the following groups were invited to comment on the draft scope, Assessment Report and the appraisal consultation document (ACD) and were provided with the opportunity to appeal against the final appraisal determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The Appraisal Committee considered clinical and cost-effectiveness evidence and a review of the manufacturer's submission by the Evidence Review Group. For clinical effectiveness, two randomised controlled trials were the main source of evidence. For cost-effectiveness, the manufacturer's model was considered.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of mannitol dry powder for inhalation for treating cystic fibrosis

Potential Harms

The most common and important adverse reactions associated with mannitol as stated in the summary of product characteristics are hyperresponsiveness to mannitol, cough, bronchospasm, exacerbation of cystic fibrosis, chest discomfort, wheezing, throat irritation, vomiting, headache and pharyngolaryngeal pain. The most clinically significant adverse reaction associated with mannitol use is haemoptysis (coughing up of blood).

Qualifying Statements

Qualifying Statements

- This guidance represents the views of the National Institute for Health and Clinical Excellence (NICE) and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

- The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the National Health Service (NHS) in England and Wales on implementing National Institute for Health and Clinical Excellence (NICE) technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.
- The technology in this appraisal may not be the only treatment for cystic fibrosis. If a NICE technology appraisal recommends use of a technology, it is as an option for the treatment of a disease or condition. This means that the technology should be available for a patient who meets the clinical criteria set out in the guidance, subject to the clinical judgement of the treating clinician. The NHS must provide funding and resources (in line with the above section) when the clinician concludes and the patient agrees that the recommended technology is the most appropriate to use, based on a discussion of all available treatments.
- NICE has developed tools to help organisations put this guidance into practice (listed below). It is available on the NICE Web site .
    - A costing statement explaining the resource impact of this guidance.

Implementation Tools

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Clinical Excellence (NICE). Mannitol dry powder for inhalation for treating cystic fibrosis. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Nov. 58 p. (Technology appraisal guidance; no. 266).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 Nov

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Clinical Excellence (NICE)

Guideline Committee

Appraisal Committee

Composition of Group That Authored the Guideline

Committee Members: Dr Amanda Adler (*Chair*), Consultant Physician, Addenbrooke's Hospital; Professor Ken Stein (*Vice Chair*), Professor of Public Health, Peninsula Technology Assessment Group (PenTAG), University of Exeter; Professor Keith Abrams, Professor of Medical Statistics, University of Leicester; Dr Ray Armstrong, Consultant Rheumatologist, Southampton General Hospital; Dr Jeff Aronson, Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford; Dr Peter Barry, Consultant in Paediatric Intensive Care, Leicester Royal Infirmary; Professor John Cairns, Professor of Health Economics Public Health and Policy, London School of Hygiene and Tropical Medicine; Mark Chapman, Health Economics and Market Access Manager, Medtronic UK; Eleanor Grey, Lay member; Dr Neil Iosson, General Practitioner; Anne Joshua, Associate Director of Pharmacy, NHS Direct London; Terence Lewis, Lay Member; Professor Ruairidh Milne, Director of Strategy and Development and Director for Public Health Research at the National Institute for Health Research (NIHR) Evaluation, Trials and Studies Coordinating Centre at the University of Southampton; Dr Rubin Minhas, General Practitioner and Clinical Director, BMJ Evidence Centre; Dr Elizabeth Murray, Reader in Primary Care, University College London; Dr Peter Norrie, Principal Lecturer in Nursing, De Montfort University; Professor Stephen Palmer, Professor of Health Economics, Centre for Health Economics, University of York; Dr Sanjeev Patel, Consultant Physician & Senior Lecturer in Rheumatology, St Helier University Hospital; Dr John Pounsford, Consultant Physician, Frenchay Hospital, Bristol; Dr John Rodriguez, Assistant Director of Public Health, NHS Eastern and Coastal Kent; Alun Roebuck, Consultant Nurse in Critical and Acute Care, United Lincolnshire NHS Trust; Navin Sewak, Primary Care Pharmacist, NHS Hammersmith and Fulham; Roderick Smith, Finance Director, West Kent Primary Care Trust; Cliff Snelling, Lay Member; Marta Soares, Research Fellow, Centre for Health Economics, University of York; Professor Rod Taylor, Professor in Health Services Research, Peninsula Medical School, Universities of Exeter and Plymouth; Tom Wilson, Director of Contracting & Performance, NHS Tameside & Glossop; Dr Nerys Woolacott, Senior Research Fellow, Centre for Health Economics, University of York

Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the National Institute for Health and Clinical Excellence (NICE) Web site .

Availability of Companion Documents

The following are available:

- Mannitol dry powder for inhalation for treating cystic fibrosis. Costing statement. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Nov. 4 p. (Technology appraisal; no. 266). Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site .
- Riemsma R, Al MJ, Armstrong N, Misso K, Allen A, Manning N, Tushabe DA, Severens JL, Kleijnen J. Mannitol dry powder for inhalation for the treatment of cystic fibrosis: a single technology appraisal. York (UK): Kleijnen Systematic Reviews Ltd.; 2011. Electronic copies: Available in PDF from the NICE Web site .

Patient Resources

The following is available:

- Mannitol dry powder for inhalation for cystic fibrosis. Information for the public. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Nov. 5 p. (Technology appraisal; no. 266). Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on January 10, 2013.

The National Institute for Health and Clinical Excellence (NICE) has granted the National Guideline Clearinghouse (NGC) permission to include summaries of their Technology Appraisal guidance with the intention of disseminating and facilitating the implementation of that guidance. NICE has not verified this content to confirm that it accurately reflects the original NICE guidance and therefore no guarantees are given by NICE in this regard. All NICE technology appraisal guidance is prepared in relation to the National Health Service in England and Wales. NICE has not been involved in the development or adaptation of NICE guidance for use in any other country. The full versions of all NICE guidance can be found at www.nice.org.uk .

Copyright Statement

Disclaimer

NGC Disclaimer

The National Guideline Clearinghouseâ„¢ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC

Inclusion Criteria.

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.